Application No.: 09/888,126
Reply to Final Office Action dated January 11, 2005

Remarks/Arguments

Summary of the Invention

The invention relates to a novel insulin-containing formulation suitable for efficient inhalation having a controllable, in particular, a rapid, release profile. This rapid release profile provides a desirable alternative to injection therapy and particularly for the treatment of diabetes in humans. The presently claimed formulation comprising particles having, by weight, approximately 60% DPPC, approximately 30% insulin, and approximately 10% sodium citrate was chosen for its superior fast acting properties, and superior stability and manufacturability. The presently claimed formulation of the invention has numerous advantages. For example the presently claimed formulation provides a rapid release profile for abbreviated residence of insulin in the lung and decreases the amount of time in which therapeutic levels of insulin are present in the local environment or systemic circulation. The rapid release of insulin provides a desirable alternative to injection therapy currently used for treating diabetes. In addition, the invention provides a method for treating a human patient in need of insulin comprising administering the presently claimed formulation via delivery to the pulmonary system wherein the high initial release of active agent, typically seen in inhalation therapy is boosted giving very high initial and rapid release of insulin. Consequently, patient compliance and comfort can be increased by reducing the frequency of dosing and avoiding the necessity to inject insulin.

Rejection under 35 USC §103(a)

In the Final Office Action, the Examiner has maintained the rejection of claims 1, 3-18, 20-39 and 41-60 under 35 USC 103(a) as being unpatentable over Patton et al. (US Patent 5,997,848) in view of Edwards (US Patent 5,985,309).

Patton is relied upon to teach dry powder insulin that can be administered to a mammal, resulting in a systemic delivery characterized by rapid absorption. The rejection states that the product can be prepared by dissolving insulin in an aqueous buffer (such as a citrate buffer) and spray drying the solution to produce amorphous

particles having "a particle size less than 10 microns." According to the rejection, preferred carriers disclosed by Patton include amino acids, such as glycine, lysine, etc. The Examiner notes that insulin and carrier concentrations can be within the broad range of 5-95%, preferably between 20-80% by weight for insulin. The Examiner notes, however, that Patton does not teach the use of DPPC as a carrier.

The Examiner turns to Edwards to establish that surfactants, such as DPPC, are known in the manufacture of insulin-containing inhalation products. The Examiner suggests that the person of ordinary skill in the art would be motivated to modify the formulations of Patton to use DPPC, as taught by Edwards, because DPPC was known to be a natural lung surfactant.

Even if the Examiner has established a prima facie case of obviousness (i.e. that it would be obvious to substitute some or all of Patton's insulin, buffer, and a carrier for Edward's DPPC), the evidence of record establishes significant unexpected results. Simply, the evidence establishes that the specific amounts of these components are critical. Thus the selection of the presently claimed approximate amounts of 60% DPPC, 30% insulin and 10% citrate combination is patentable over the myriad of possible combinations derived from the combination of Patton and Edwards. However, in the Final Office Action, the Examiner maintains the obviousness rejection even in view of Applicant's evidence of significant unexpected results in the form of a Rule 132 affidavit.

It is well settled that unexpected results must be established by factual evidence. *In re Lindner*, 173 USPQ 356 (CCPA 1972). Applicants have provided this factual evidence in the form of a Rule 132 affidavit. It is also well settled that proof of unexpected properties may be in the form of direct or indirect comparative testing of the claimed compounds and the closest prior art. *In re Payne*, 203 USPQ 245, 256 (CCPA 1979) and *In re Grasselli*, 218 USPQ 769 (CAFC 1983).

A proper showing of unexpected results will rebut a prima facie case of obviousness. *In re Fenn*, 639 F.2d 762, 208 USPQ 470 (CCPA 1981). In *In re Fenn*, the court approved the use of declaratory evidence showing an indirect comparison between the appellant's diaphragm prepared according to appellant's specification and the

swelling characteristics of the closest prior art which was sufficient to provide an indirect showing of unexpected superiority sufficient to rebut a *prima facie* case of obviousness.

The Examiner does not appear to contest the sufficiency of Applicant's declaratory evidence or the unexpected superiority of the results provided therein other than to state that the declaratory evidence is "not found persuasive". The Examiner has instead, simply maintained the obviousness rejection without any articulated rationale or evidentiary support as to *why* Applicant's comparative data is insufficient to rebut the Examiner's obviousness objection. MPEP 2144.08 (III). On page 3 of the Final Office Action, the Examiner states that:

> "[the Declaration] was not found persuasive because while it provided data on the stability of certain concentration ranges, it did not overcome the prior art rejections. While applicant insists that the specific amounts of each ingredient makes the formulations stable, the concentration ranges fall within the ranges disclosed by the references and thus it is considered that the prior art of record meets the claimed limitations."

In the MPEP, 2144.05 (III) it states that "[a]pplicants can rebut a *prima facie* case of obviousness based on overlapping ranges by showing the criticality of the claimed range". Applicant's 132 affidavit clearly shows that the criticality of the presently claimed formulation (not a *range* of formulations as described by the Examiner, but instead a superior *single species* of formulation), having particles comprising, by weight, approximately 60% DPPC, approximately 30% insulin and approximately 10% sodium citrate possesses unexpected properties as compared to formulations that are even *closer* than those of the combination of prior art cited by the Examiner. The Patton reference cited by the Examiner discloses that insulin and carrier concentrations can be within the broad range of 5-95%, preferably between 20-80% by weight for insulin. Patton makes no specific mention of the range of aqueous buffer. The Examiner relies on Edwards to provide DPPC as a carrier but no preferred DPPC range is disclosed in Edwards. In the Examples, Edwards describes a number of different DPPC-containing formulations, including formulations containing 10%, 33% and 60% by weight DPPC. Clearly, the combination of cited references provides so many possible combinations of formulations, that evidence of unexpected results (provided by Applicants 132 affidavit) for a *single*

combination (species) of formulation necessitating the selection of three specific components in a single specific combination, within the prior art ranges cited by the Examiner is more than sufficient to overcome any *prima facie* case of obviousness in view of the combined references. For example in *In re Ruschig*, 145 USPQ 274 (CCPA 1965), the court was faced with claimed species of compounds that fell into the general class of sulfonylureas, known to be a large class of compounds. The compounds singled out for patenting had been discovered by appellants as a part of their systemic and extensive research, to possess the ability to lower the level of blood sugar, for use in treating diabetes but also because of other desirable properties that they possess in connection with such use. Appellants provided an affidavit of record indicating that as compared with compounds of similar structure to the claimed compounds, the claimed compounds are distinguishable based on a number of properties including shelf-life, handling and that they also have no bacteriostatic action as compared to similar anti-diabetic compounds. The *Ruschig* court reversed the Patent Office's obviousness rejection and citing *In re Lunsford* 140 USPQ 425, 427 stated that:

> "and in *In re Lunsford*, 51 CCPA 1000, 327 F.2d 526, 140 USPQ 425, 427, wherein Judge Martin, speaking for the court, finding an "unobvious property inherent in the claimed compounds" sufficient to overcome a showing of very close structural obviousness, said "there is no basis in law for ignoring any property," and in *In re Ward*, 51 CCPA 1132, 329 F.2d. 1021, 141 USPQ 227, 228, wherein the court said:
>
> * * * claims to chemical compounds are drawn to more than structural formulae. They define the compounds themselves and compounds possess properties which must be considered along with the formulae.
>
> Here the esters might appear to be obvious in terms of the concept of their structure but that is only half the game. There remains the consideration of the properties of the esters. * * * That unexpected property cannot be ignored in the determination of obviousness of the claimed esters *as substances* and not as structural formulae."

The case law permits patenting a species even where the prior art generically discloses it based upon evidence of unexpected results. The MPEP states that patenting within ranges is permissible with sufficient evidence of unexpected results. MPEP 716.02 (d).

Clearly, Applicants showing of unexpected enhanced stability and manufacturability of the presently claimed *specific* formulation is sufficient to overcome any *prima facie* case of obviousness in view of the potentially infinite combinations of formulations provided by the ranges disclosed in the cited combination of Patton and Edwards. Applicants have shown unexpected and enhanced stability as compared to formulations that are even *more* similar to those of cited prior art in their 132 affidavit.

With regard to the Examiner's statement that "[i]t is also noted that stability is a property of the formulations", Applicants are unclear as to what the Examiner's point is here. If the Examiner is asserting that because stability is an inherent property of the formulations, unexpected superiority of that property is insufficient to overcome obviousness, a wealth of case law contradicts the Examiner's position.

For example in *In re Chupp*, 2 USPQ2d 1437, the Appellant (Chupp) submitted a declaration discussing the results of tests comparing the herbicidal activity of the claimed compound with that of the closest prior art compounds and with two commercial herbicides, to rebut the prima facie case of obviousness. The tests compared the compounds' ability to control two weeds and it was undisputed in the record that the claimed compound gave superior results. The board deemed the declaratory evidence insufficient to rebut the case of obviousness claiming the compound had no new or unexpected property; it possesses the same property as the prior art compounds. The court, citing *In re Papesh*, 137 USPQ 43 (CCPA 1963), stated that:

> "The Papesch court held, "From the standpoint of patent law, a compound and all of its properties are inseparable; they are one and the same thing" (citation omitted). Under the Papesch doctrine, evidence of unobvious or unexpected advantageous properties may rebut a prima facie case of obviousness based on structural similarities [citation omitted]. Such evidence may include data showing that a compound is unexpectedly superior in a property it shares with prior art compounds. E.g. *In re Lunsford*, 357 F2d 380, 148 USPQ 716 (CCPA 1966). "

The court in *In re Chupp* went on to cite another case, *In re Ackerman*, 170 USPQ 340 at 343 (CCPA 1979) for additional precedent indicating that "evidence that a compound is unexpectedly superior in one of a spectrum of common properties, as here, can be enough to rebut a prima facie case of obviousness". Although the Solicitor in *Chupp* tried to

argue that *Chupp*'s declaratory evidence did not show an unexpected difference in the properties in view of the prior art, the court disagreed. The court noted that the record did not support the Solicitor's assertion that the claimed compound's superior properties would have been expected, and to support the court's position, the court cited *In re Blondel*, 499 F2d 1311,182 USPQ 294 (CCPA 1974) (reversing rejection of claims to compounds which prior art suggested would have longer lasting pharmacological activity, where actual increase was beyond reasonable expectations).

Similarly, in the present application, the Examiner has provided no evidence that the superiority of the stability properties of the claimed formulation as described in Applicant's 132 affidavit are in any way predicted or suggested in the cited combination of prior art. Neither reference discusses the criticality of the amounts of each component of the formulation to provide superior stability and manufacturability.

Perhaps the Examiner is concerned by the fact that the evidence of record compares, not the specific formulations of Patton, but more relevant or closer formulations provided by the Applicant. The courts have looked favorably upon indirect evidence that is even closer than that of the prior art. For example, in *In re Grasselli, supra*, an applicant claiming a catalyst showed unexpected results when he tested the claimed catalyst with the most similar catalysts, which were his own, that were claimed in broader claims. The court found that none of the prior art cited by the examiner described a catalyst more similar to the claimed catalyst than the applicant's own catalysts claimed in the broader claims. See 218 USPQ at 779. The *Grasselli* court found this indirect showing of superiority over the prior art sufficient to rebut the Examiner's showing of obviousness.

Similarly, in the present application, neither Patton nor Edwards cited by the Examiner, provides an example of a formulation comprising all the components of the presently claimed formulation, i.e. DPPC, insulin and sodium citrate. Applicants have instead provided formulations for comparison that are *closer* than those of the cited combination of prior art. The Declaration shows that six formulations that differ solely in the relevant amounts of the hydrophobic component (e.g., DPPC), citrate and insulin can have substantial differences in stability and manufacturability. Notably, increasing the

amount of insulin in the formulation from 10% to 30%, with a corresponding decrease in the lipid (i.e. "hydrophobic") component, DPPC, dramatically and unexpectedly improved the solubility of the total solids in the spray drying solution. The improved solubility of total solids is critical to the stability, manufacturability and ultimately, the desired performance of the formulation. Therefore, Applicants have met the burden of providing comparative data with the closest prior art by making an indirect showing of unexpected superiority using prior art that is even closer than the prior art provided by the Examiner.

In view of the above arguments and citation of case law, Applicant's submit that they have provided evidence in the form of a 132 affidavit sufficient to meet their burden of establishing unexpected and significant properties of the presently claimed formulation. Thereby, Applicants submit that they have rebutted any *prima facie* case of obviousness that the Examiner may have established by the combination of cited references and respectfully request that the rejection under 35 U.S.C. §103 over Patton in view of Edwards be withdrawn.

Although Applicants' remarks above are limited to Applicants' evidence for rebutting a prima facie case of obviousness over Patton in view of Edwards, Applicants continue to maintain that the Examiner has not in fact established a *prima facie* case of obviousness for all of the reasons of record so far in this application. However, in order to reduce the number of issues if an appeal becomes necessary, Applicants' position is that Applicants' declaratory evidence showing unexpected results overcomes any *prima facie* case of obviousness that Examiner may have established.

Double Patenting Rejection

The Examiner has also rejected Claims 1, 3-18, 20-39 and 41-60 under the doctrine of obviousness-type double patenting over copending Serial No. 10/179,463 in view of Patton. Applicants disagree with the Examiner's reasoning for maintaining the obviousness-type double-patenting rejection outlined in the Final Rejection. The claims of the copending application Serial No. 10/179,463, claim a formulation which is different from the formulation of the present claims. The copending application and the

present application claim two different species of formulation, each having its own unique set of properties. Therefore, the double patenting rejection is improper. Notwithstanding, in order to reduce the number of issues if an appeal becomes necessary, Applicants are filing herewith a terminal disclaimer over co-pending application serial number 10/179,463.

Conclusion

In light of the foregoing amendments and remarks, Applicants believe the claims are in condition for allowance and a prompt notice to that effect is requested. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (978) 251-3509.

Respectfully submitted,

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